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United States Patent [19]**Blum**[11] **Patent Number:** **6,132,724**[45] **Date of Patent:** **Oct. 17, 2000**[54] **ALLELIC POLYGENE DIAGNOSIS OF
REWARD DEFICIENCY SYNDROME AND
TREATMENT**[75] **Inventor:** **Kenneth Blum**, San Antonio, Tex.[73] **Assignees:** **City of Hope National Medical
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of Texas System AMD Board of
Regents**, Austin, Tex.[21] **Appl. No.:** **09/069,886**[22] **Filed:** **Apr. 29, 1998**[51] **Int. Cl.⁷** **A61K 35/78**[52] **U.S. Cl.** **424/195.1; 514/188; 514/561**[58] **Field of Search** **514/188, 561;
424/195.1**[56] **References Cited****U.S. PATENT DOCUMENTS**

4,650,789	3/1987	Pollack	514/23
4,761,429	8/1988	Blum et al.	514/561
4,897,380	1/1990	Pollack et al.	514/23
5,013,752	5/1991	Dobbins	514/505
5,019,594	5/1991	Wurtman et al.	514/561
5,164,384	11/1992	Paul	514/188
5,189,064	2/1993	Blum et al.	514/561
5,210,016	5/1993	Blum et al.	435/6
5,500,343	3/1996	Blum et al.	435/6
5,543,405	8/1996	Keown et al.	514/188
5,550,021	8/1996	Blum et al.	435/6

FOREIGN PATENT DOCUMENTS

WO 87/00430	1/1987	WIPO
8701590	3/1987	WIPO
WO 95/11034	4/1995	WIPO
WO 98/48785	11/1998	WIPO

OTHER PUBLICATIONS

Abraham and Dufy, "Computed EEG abnormalities in panic disorder with and without premorbid drug abuse," *Biol. Psychiatry*, 29:687-690, 1991.

Accili et al., "A new look at D₃ receptors," *Mol. Psychiatry*, 1:93-94, 1996.

Adams et al., "Neuropsychological deficits are correlated with frontal hypometabolism in positron emission tomography studies of older alcoholic patients," *Alcohol Clin. Exp. Res.*, 17:205-210, 1993.

Allen and Gorski, "Sex differences in the bed nucleus of the stria terminalis of the human brain," *J. Comp. Neurol.*, 302:697-706, 1990.

Altura, B.M. and Gebrewold, A. "Pyrrolidine Dithiocarbamate Attenuates Alcohol-Induced Leukocyte-Endothelial Cell Interaction and Cerebral Vascular Damage in Rats: Possible Role of Activation of Transcription Factor NF- κ B in Alcohol Brain Pathology," *Alcohol* 16:25-28, 1998.

Amit and Brown, "Actions of drugs of abuse on brain reward systems: A reconsideration with specific attention to alcohol," *Pharmacology Biochemistry and Behavior*, 17:233-238, 1982.

Aoki, Go, Venkatesan, Kurose, "Perikaryal and synaptic localization of alpha-2A-adrenergic receptor-like immunoreactivity," *Brain Res.*, 650:181-204, 1994.

Arcot, Wang, Weber, Deininger, Batzer, "Alu repeats: a source for the genesis of primate microsatellites," *Genomics*, 29:136-144, 1995.

Arndt-Jovin, Udvardy, Garner, Ritter, Jovin, "Z-DNA binding and inhibition by GTP of *Drosophila* topoisomerase II," *Biochemistry*, 32:4862-4872, 1993.

Arnsten, Steere, Hunt, "The contribution of α_2 -noradrenergic mechanism to prefrontal cortical cognitive function. Potential significance for Attention-Deficit Hyperactivity Disorder," *Arch. Gen. Psychiatry*, 53:448-455, 1996.

Asghari et al., "Modulation of intercellular cyclic AMP levels by different human dopamine D₄ receptor variants" *J. Neurochem*, 65:1157-1165, 1995.

Ashani, Grunwald, Kronman et al., Roles of tyrosine 337 in the binding of Huperzine A to the active site of human acetylcholinesterase, *Mol. Pharmacol.*, 45:555-560, 1994.

Ashani, Peggins, Doctor, "Mechanism of inhibition of cholinesterase by Huperzine A," *Biochem. Biophys. Res. Commun.*, 184:719-726, 1992.

Aston-Jones et al., "Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggest a role in vigilance" *Progress in Brain Res.*, 88:501-520, 1991.

August and Garfinkel, "Behavioral and Cognitive Subtypes of AD-HD," *J. Am. Acad. Child Adoles. Psychiatry*, 28(5):739-748, 1989.

August et al., "Familial subtypes of childhood hyperactivity" *J. Nerv. Ment. Dis.*, 171:362-368, 1972.

Bain, et al., "Naloxone attenuation of the effect of cocaine on rewarding brain stimulation," *Life Sciences*, 40:1119-1125, 1986.

Balfour and Fagerström, "Pharmacology of nicotine and its therapeutic use in smoking cessation and neurodegenerative disorders," *Pharmac. Ther.*, 72:51-81, 1996.

Ballidin et al., Further neuroendocrine evidence for reduced D₂ dopamine receptor function in alcoholism, *Drug Alcohol Dep.*, 32:159-162, 1993.

(List continued on next page.)

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Enhancement of attentional processing is attained by administration of an endorphinase inhibitor or enkephalinase inhibitor and optionally, a dopamine precursor, or a serotonin precursor, a GABA precursor, or an endorphin or enkephalinase releaser, or certain herbal compounds including *Rhodiola rosea* extract (Pharmaline) and/or Huperzine. These components promote restoration of normal neurotransmitter function and the components combined enhance the release of dopamine at the nucleus accumbens and are non-addictive. Use of the dopamine precursors L-phenylalanine, or L-Tyrosine, the enkephalinase inhibitor D-phenylalanine, and/or the serotonin precursor -hydroxytryptophan and a natural acetylcholinesterase inhibitor and chromium salts (i.e. picolinate, nicotinate, etc.) is especially preferred, but not limited to assist in relieving symptoms associated with brain phenylalanine deficiency.

9 Claims, 8 Drawing Sheets